HOW SIMILAR IS BIOSIMILAR?

This update, written by healthcare professionals for healthcare professionals, aims to give you all the information you need to understand what biosimilars are, what evidence there is and how to communicate that to patients.

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THE EMERGENCE OF THE FIRST BIOSIMILARS IS POSSIBLY ONE OF THE MOST FASCINATING AND POLITICALLY INTRIGUING DEVELOPMENTS WE HAVE EVER SEEN IN THE FIELD OF IBD.

Dr Matthew Johnson, Consultant Gastroenterologist

March 2015 sees the introduction of the first infliximab biosimilar into the British market, and healthcare professionals have many questions on the use of this new form of biological medication.

Over the course of the last 30 years, the sales of biological agents such as *infliximab* and *adalimumab* have grown at twice the rate of the rest of the pharmaceutical market, and so this new product is an interesting challenge to the established biological producers.

As with any new medicine there will be a period of wary uncertainty and learning, followed by a trial period, before it will be used with confidence as an equal within the drug armoury.

The **European Medicines Association (EMA)** has already authorised the use of 17 biosimilars, used across a range of specialties, and there are two brands of *infliximab* available in the UK.

Interestingly, they are the same product, made in the same factory by **South Korea's Celtrion Healthcare Inc**, but are distributed by different companies: *Remsima* by **NAPP** in the UK and *Inflectra* by **Hospira** in the Republic of Ireland.

Throughout Europe the same product has different names and is distributed by a range of companies.

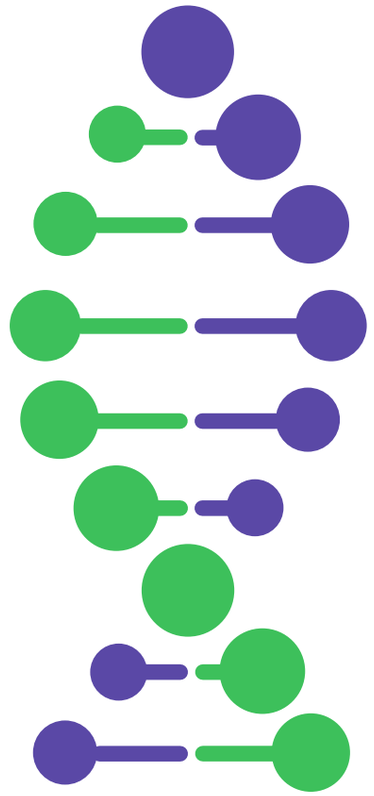
Interesting times lie ahead. The increase in competition and reduction in price offered by the biosimilar distributors can only be a good thing in the long-term for the patients.

The question most gastroenterologists will have to ask themselves is how convinced they are by the data, and if they are confident to start using these products.

Many will not be prepared to prescribe them until there is more clinical data in IBD. Others may be convinced by the similarity studies and be happy to consider it.

Celtrion Healthcare Inc is the first to launch its *infliximab* biosimilar in the UK, but others are coming with a whole new collection of distributors and trade names.

What's more, as soon as you thought you had it mastered, remember the patent for *adalimumab* is due to run out within the next three years.



WHAT IS A BIOSIMILAR?

Biological medications like *infliximab* and *adalimumab* are created from living cells, and their complex structures are based on naturally occurring substances such as antibodies.

Biosimilars are biological agents that have been created to be similar to already authorised biological medicines: in other words, they are a generic form of a biological treatment.

These copy versions must be similar in their physicochemical characteristics, efficacy and safety, based on comprehensive comparability assessments. A generic therefore is an original product or one that contains the same active substances as the original reference medicine.

> "The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods." The EMA.[1]

[1]EMA. Questions and answers on biosimilar medicines (similar biological medicinal products). EMA/837805/2011

Biosimilars by definition are similar to their originator product, but they are not bio-identical. Minor differences include micro-heterogeneity, where the act of manufacturing creates different forms of the same protein, and post-translational modification, where the packaging of a molecule can vary slightly in its glycosylation, methylation, oxidation and deamination.

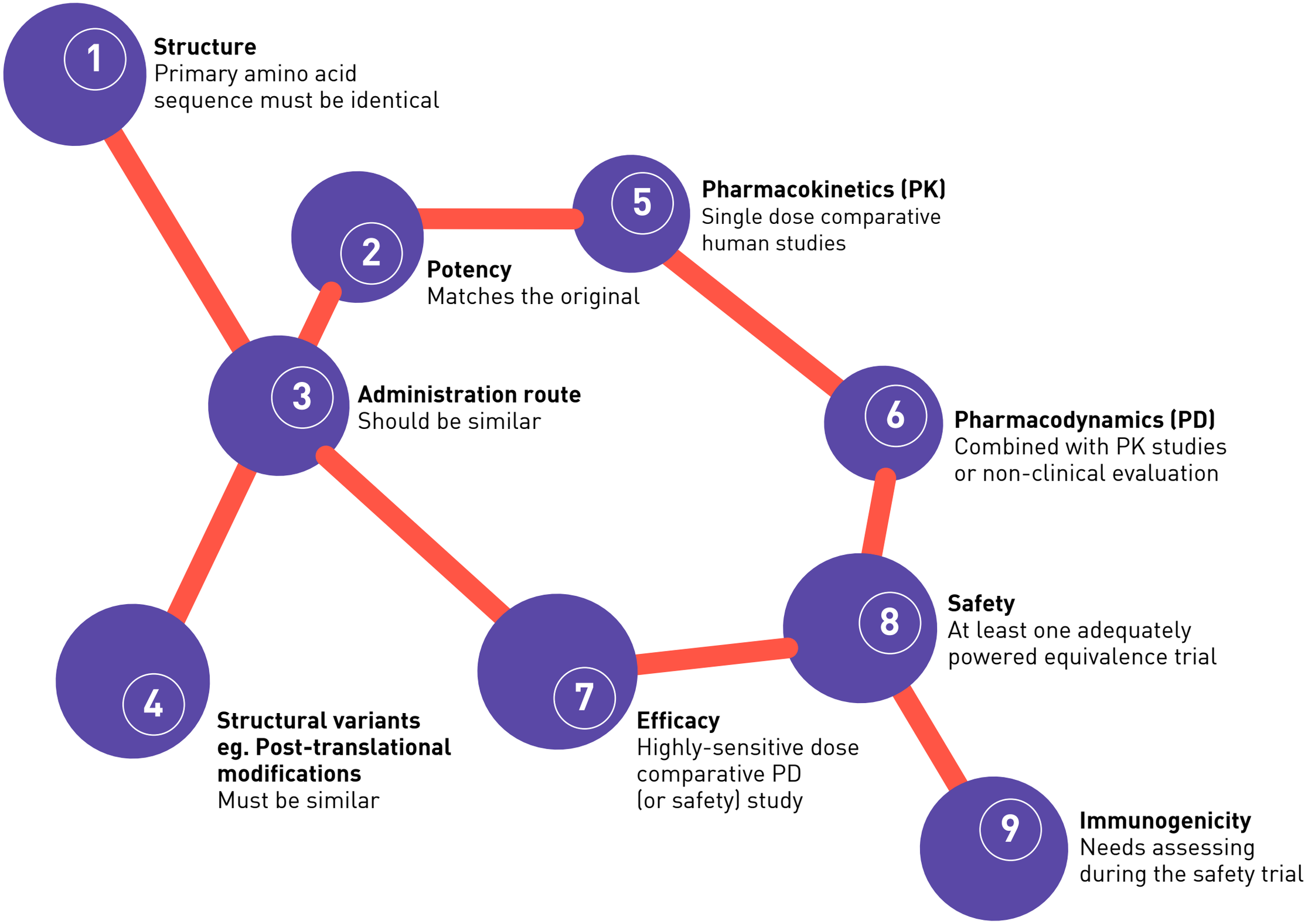
Even though the copy of the original protein may be identical, variations in its packaging could lead to changes in the way protein is presented to a receptor, affecting both its efficacy and safety profile.

Also, the originator molecules themselves are difficult to replicate and manufacture, and are themselves variable.

In this way the *infliximab* originator ***Remicade,*** which is produced by **MSD** in the UK, has undergone 37 post-approval manufacturing changes, meaning the product available today could itself be deemed a biosimilar of its original.

For manufacturers to gain approval for generic drugs they need to establish bioequivalence to the originator product using pharmacokinetic data. For a complex monoclonal antibody biosimilar to be approved, comprehensive comparative studies need to be performed to establish biosimilarity with the originator product.

The regulatory requirements for the EMA to accept a biosimilar as a suitable alternative include nine key assessments.



WHAT EVIDENCE IS THERE FOR INFLIXIMAB BIOSIMILARS?

There will be a degree of minor natural variability during reproduction. For a biosimilar to be approved, however, differences between biosimilar and the original reference medicine must be negligible, with no effect on safety or efficacy.

Assessments can be performed by comparing batches after manufacturing changes and comparing batches produced by different sites. Providing similarity can be proven through these stringent assessments, the biosimilar can apply for extrapolation of the clinical uses and key indications of its originator molecule.

In this way the biosimilar manufacturers can use, at least in part, clinical efficacy and safety data of the original product.

In Europe, such extrapolation is decided on a case-by-case basis by the **Committee for Human Medicinal Products (CHMP)** of the **EMA**.

Extrapolation can be considered when the biosimilar has been shown to be equivalent in efficacy and safety with one key clinical indication. So far clinical trials using infliximab biosimilars (CT-P13) have looked at effectiveness in two conditions: rheumatoid arthritis in the PLANETRA study[1] and ankylosing spondylitis, in the PLANETAS study.[2]

The **EMA** allowed the license to be extrapolated to cover inflammatory bowel disease and psoriasis, as it identified no pharmacokinetic or safety issues specific to IBD or psoriasis that weren't seen in the rheumatoid arthritis or ankylosing spondylitis.

There were some differences noted between the biosimilars and *Remicade* in these two trials.

[1]Yoo DH. Ann Rheum Dis 2013;72:1613-20.
[2]Park W. Ann Rheum Dis; 2013:72;1605-12.

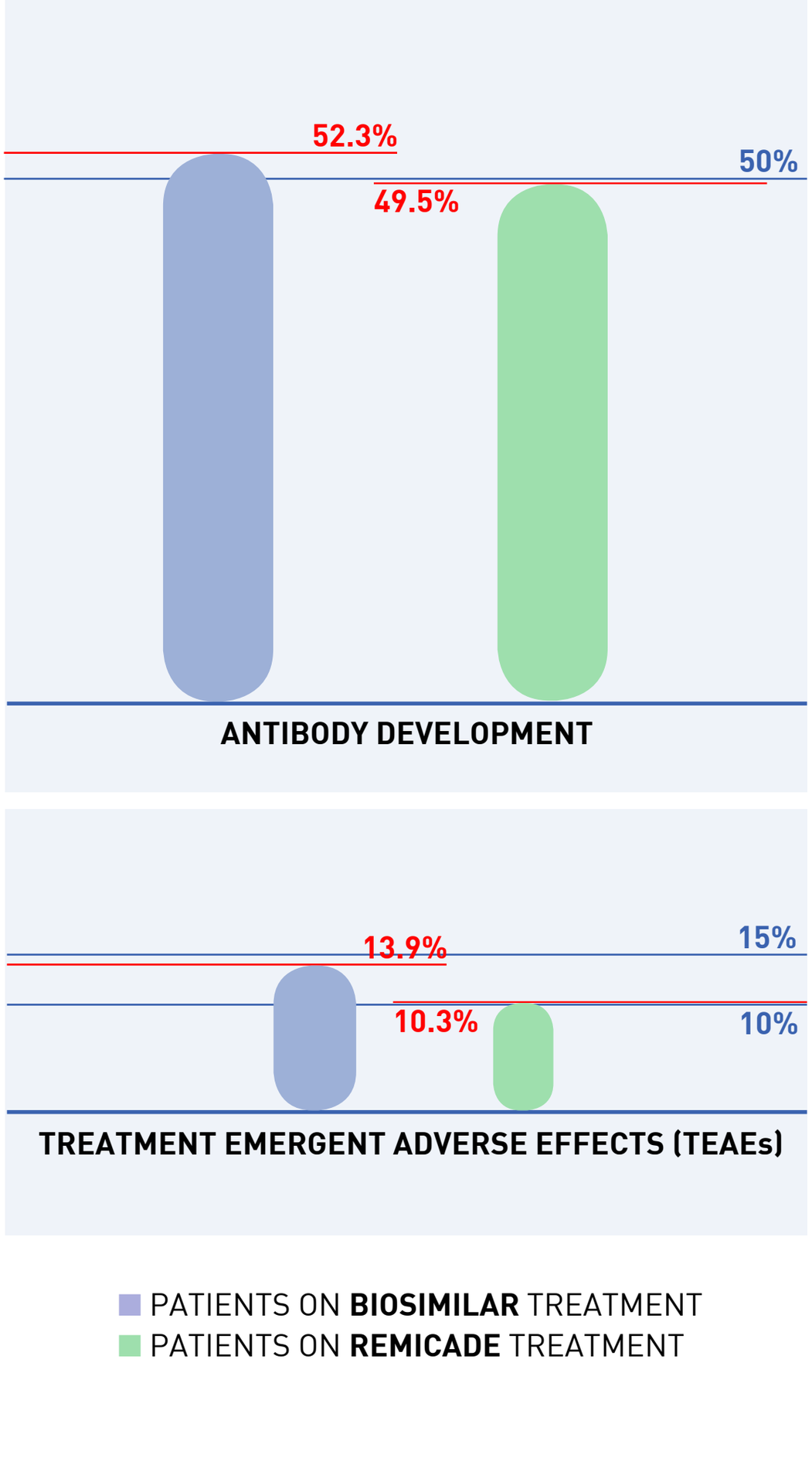
PLANETRA

The PLANETRA trial looked at moderate to severe rheumatoid arthritis patients who were not fully controlled on *methotrexate*. It was a phase three, randomised, double blind trial of 606 people, which ran for 54 weeks, with an extension study running up to 102 weeks. In total, 304 patients were randomised to receive *Remicade* and 302 the biosimilar, CT-P13 infliximab, at a dose of 3mg/kg at week 0, two and six. This was followed by further infusions every eight weeks.

The regimen ran concomitantly with *methotrexate* 12.5-25mg / week and *folic acid* >5mg / week. This was completed by 455 patients. There was a drop-out rate of 25%.

A total of 302 patients decided to continue on the study after 54 weeks, using just CT-P13 until 102 weeks. This included 158 already on the biosimilar, while the 144 who had been on *Remicade* were asked to switch to CT-P13.

The clinical outcomes were similar, however three cases in the CT-P13 group developed active TB, which highlighted the need to screen before starting any patient on biological therapy. Antibodies were found to occur at a slightly higher frequency in the biosimilar group: 52.3% verses 49.5% in the *Remicade* group. In addition, the number of serious treatment emergent adverse events (TEAE) were slightly higher in the biosimilar group, at 42, or 13.9%, compared to 31, or 10.3% of the *Remicade* patients.



PLANETAS

PLANETAS was a similar but smaller trial, starting with 250 patients: half on *Remicade* and half on CT-P13. It was a phase one, randomised, double blind trial that ran for 54 weeks.

It was completed by 210, and 174 continued on an extension, only using CT-P13, up to 102 weeks. Of those on the extension trial, 88 were already on CT-P13 and 86 had to switch from *Remicade* to the biosimilar. These patients had moderate to severe ankylosing spondylitis with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of four or more.

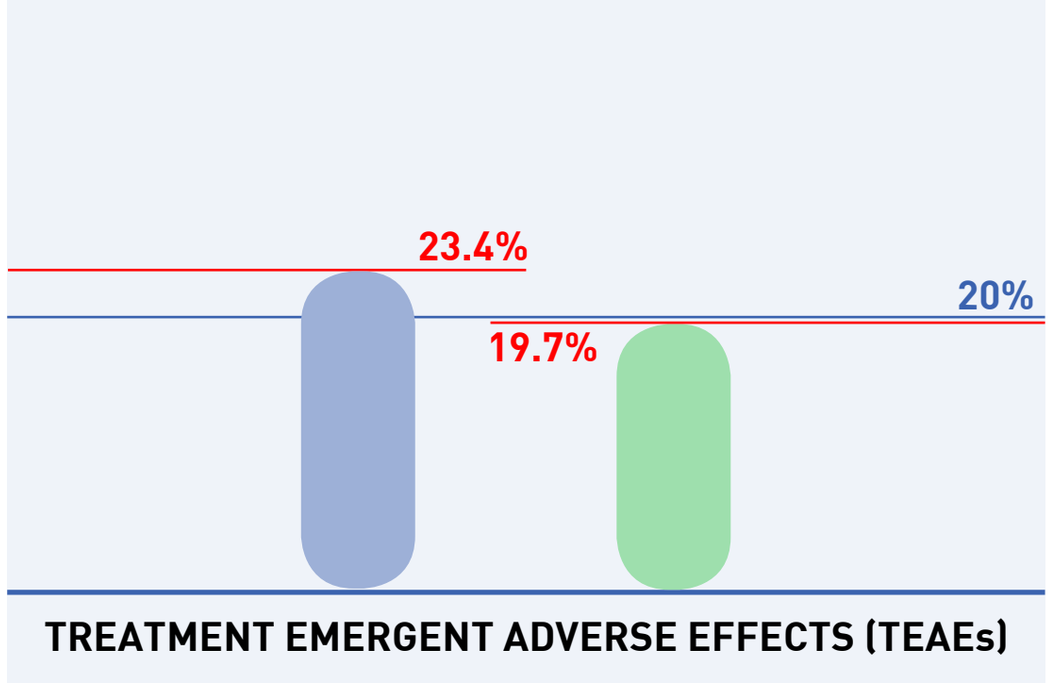
The results for this trial were similar, however higher levels of aggregates and lower levels of glycosylation (reduced afucosylated glycans) were noted in the biosimiar group.

Despite this there were fewer anti-infliximab antibodies seen in the biosimilar (CT-P13) group with 22.9% versus 26.7% in the *Remicade* group at 54 weeks. At week 54 there were TEAEs in 30, or 23.4% of patients on CT-P13 compared to 24 or 19.7% of those on *Remicade*.

This became more evident in the extension study where >1 TEAE were seen in the *Remicade* group who were made to switch to biosimilar (60 or 71.4%) compared to those who were maintained on the same biosimilar (44 or 48.9%).

A similar trend was noted in the serious STEAEs. At week 102, the switch group were found to have accumulated more infections (29 or 34.5%) compared to the biosimilar maintenance group (23 or 25%). The switch group also started to accumulate infections to a greater degree than 29 (34.5) compared with 23 (25%) in the maintenance group.

Based on these two clinical studies, *Remsima* has been allowed to extrapolate its clinical usage to include psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.



CONCERNS

Immunogenicity is of some concern. All monoclonal antibody therapies can trigger antibody formation, which increases the risks of infusion reactions and long-term efficacy.

There are multiple factors including the nature of the drug, impurities, excipients, stability, administration route, dosing regimes, patients' characteristics, vials and stoppers.

We do not know the long-term adverse events profile of these biosimilars, so physicians must use trade names so adverse reactions can be assigned to the correct product.

WHAT ARE THE COST DIFFERENCES?

Dr Matthew Johnson, Consultant Gastroenterologist

At Luton and Dunstable Hospital we have 64 patients on *Remicade*, costing approximately £700,000 a year, but our use of biological agents is rapidly increasing.

There will be increasing pressure throughout the UK to reduce the costs of biological agents. **NICE** has updated the use of biological agents for moderate to severe ulcerative colitis, and CCGs will be keen to encourage clinicians to prescribe the cheapest option.

There are clear financial savings to be made, but also concerns that patients could see their prescription cycling between different brand names depending on who is doing the "deal of the month".

In the early stages there may well be clinical service "gain share", as companies offer hospitals incentives such as additional IBD nurse support if they switch to or stick with a particular brand.

Such benefits need to be weighed up against the potential of damaging confidence in the doctor/patient relationship if things go wrong.

Biosimilars are big money. The list price for *Remicade* is **£419** per vial, but its selling price is often lower, in the region of **£367**.

The East of England recently ran its first regional contract tender, and *Remsima* came out at **£257– £297**, *Inflectra* at **£210**. Other regional tenders are expected, in which *Remsima* is likely to be more competitive.

Switching between the original *Remicade* product to a biosimilar is expected to offer considerable savings – within Europe alone around **€33.4 billion** by 2020.

Celltrion Inc. has been the first company to get its biosimilar mAb anti-TBF agent approved by the **EMA**, and if the company and distributors reduce the cost by a third, this would lead to significant cost savings for CCGs.

If however, the CCGs allow each Trust to enjoy some of these gains IBD services will improve.

From a patient's perspective, if their CCG saves one-third, 33% more patients could have the benefits of *infliximab*, for the same cost.

SAVINGS WITHIN EUROPE:
€33.4 BILLION BY 2020

£210
(lowest) COST OF **BIOSIMILAR** PER VIAL

£419
(highest) COST OF **REMICADE** PER VIAL

HOW DO WE SHARE THIS INFORMATION WITH PATIENTS?

By Helen Ludlow, IBD CNS

Patients are likely to have reservations about biosimilars.

The majority of patients today use the internet for information about their medical condition and treatment options. It is vitally important, therefore, that patients and HCPs have informative discussions about biologic and biosimilar drugs in order to enable joint decision making and improve patient concordance for their treatment.

HCPs, nurses in particular, can address concerns their patients may have by being aware of these frequently asked questions, and how to answer them without medical jargon.

What is a biological drug?

Our bodies naturally produce a protein known as TNF-alpha (tumour necrosis factor-alpha). This protein is part of the immune system and works by sending out signals to start the required response to infection, i.e., inflammation.

Inflammation is a normal and healthy response to infection and is part of the healing process, but in conditions such as IBD and arthritis, it is thought the body over-produces this protein. The immune system over-reacts and the result is excess inflammation.

In IBD, the gastrointestinal tract becomes inflamed and in arthritis it causes inflamed joints.

Biologic drugs such as *infliximab* work by binding to the TNF-alpha protein, and this stops them from causing an inflammatory response and, subsequently, inflammation.

What is a biosimilar?

Until recently, only certain pharmaceutical companies have been allowed to make biologic drugs as they owned the licence to make them exclusively. That licence has now expired and so other companies are able to start to produce them.

Biosimilars are chemically the same as the original biologic and are created to be the same, or similar to, existing products.
The safety of any human medication is a top priority and any new drugs must meet strict criteria, even the drugs that are "copies" of or 'similar' to existing drugs.

The **EMA** said: *"The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods."*

Are biosimilar drugs suitable to treat IBD?

As the exclusive production licence for infliximab in treating IBD has only recently expired, there are limited trial data in this particular disease. There is more information known about using biosimilars in rheumatoid arthritis and ankylosing spondylitis.

These trials did not show any significant difference in effectiveness or safety between the biologic and biosimilar products.
The **EMA** has, therefore, allowed the licence for these biosimilar drugs to be used in IBD.

Why use biosimilars?

The prevalence of inflammatory diseases such as IBD is rising across the world and treating them with biologics can benefit patients by improving their symptoms and quality of life.

It is hoped that this new wave of drugs will be able to help groups of patients who have not previously qualified for them.

Biologics are expensive and incur major costs.
It is simply not possible to continue to treat the rising number of patients with the original and more costly drugs.

By using biosimilar versions, the **NHS** will be able to continue treating everyone currently receiving them, and, in future, will allow a greater number to benefit.

ASSOCIATION OF BRITISH PHARMACEUTICAL INDUSTRY (ABPI)

The ABPI makes seven recommendations for action by regulators, HTA agencies, NHS commissioners and NHS healthcare professionals who prescribe or dispense these medicines.

1. All biological/ biosimilar medicines should be prescribed by brand name and not by International Non-proprietary Name (INN);
2. Automatic substitution is not appropriate for biological medicines, including biosimilars;
3. Patients should be kept fully informed about their medication and consulted about changes to their treatment;
4. The SmPC for a biosimilar medicine should clearly indicate the source of information contained within it, such as relevant data from its clinical development programme and clinical data derived from the originator or reference biological medicine;
5. Biosimilar medicines should be subject to health technology assessment processes in the UK;
6. Tenders for biological medicines should not seek to source a single product;
7. Extrapolation of indications for biosimilar products should be evaluated by regulators on a case-by-case basis.

To read the full document, go to **www.abpi.org.uk**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE)
BIOSIMILARS POSITION STATEMENT

1. **NICE** will consider similar biological medicinal products notified to it by the National Institute for Health Research Horizon Scanning Centre for referral to the Technology Appraisal topic selection process;
2. These products will usually be considered in a Multiple Technology Appraisal in parallel with their reference products;
3. In other circumstances, where a review of the evidence for similar biological medicinal products is necessary, **NICE** will consider producing an 'Evidence summary: new medicine';
4. **NICE** technology appraisals will use the name of the active drug substance, including reference products and brand named similar biological medicinal products in its documentation to inform clinical decision making and to reflect the remit received from Ministers;
5. A technology appraisal remit referred to **NICE** by the **Department of Health** in England, and all resulting guidance, can be applied to relevant, licensed biosimilars that subsequently appear on the market;
6. Evidence summaries will use brand names because substitutability and interchangeability cannot be assumed. Evidence summaries do not make recommendations so the decision on the choice of biosimilar or originator biologic for a patient rests with the clinician in consultation with the patient.

For more information on this, go to **www.nice.org.uk**

BRITISH SOCIETY OF GASTROENTEROLOGISTS (BSG) STATEMENT ON BIOSIMILAR DRUGS

The BSG welcomes the introduction of new agents to treat patients with IBD.

Drugs that increase treatment options and generate price competition that ultimately benefit patients are necessary and desirable. The healthcare economy is finite and patient access to biologics, in particular, limited by the **NICE** models of cost-effectiveness.

Anti-TNF biosimilar drugs appear to provide a new means of treating patients with agents that resemble drugs in current use: we note the position of **EMA** on the similarity. Manufacturing processes have changed since *infliximab (Remicade)* was launched and the drug is not necessarily identical to the one in the original trials. *Remicade* may already be its own biosimilar.

Most anti-TNF mAbs have been shown to be effective in both Crohn's disease and ulcerative colitis. It is reasonable to suppose that biosimilar anti-TNFs will also be effective. The target epitopes appear to be the same although the post-translation modification by bacteria may differ: such details are not in the public domain.

There is evidence that biosimilar anti-TNFs are effective in some rheumatological diseases. There is no published evidence at all in IBD. The IBD Committee is aware of three studies that will begin to fill this void [ClinicalTrials.gov Identifier: NCT02066272 (SATIMOS), ClinicalTrials.gov Identifier: NCT02148640 (Nor-Switch), and ClinicalTrials.gov Identifier: NCT02096861 - Demonstrate Non-inferiority in Efficacy and to Assess Safety of CT-P13 in Patients With Active Crohn's Disease.]

At present, we urge caution until we have more data. We recommend:

1. Prescribing by brand name e.g. use *Remicade* rather than *infliximab*;
2. Patients already on therapy, should avoid switching from parent drug to biosimilar, or vice versa, at least until we have safety data;
3. A registry of all biological use in IBD to capture safety data, rare and new side effects. We recommend the IBD Registry (www.ibdbiologicsaudit.org);
4. Discussion with patients about the choice of anti-TNF;
5. A substantial discount in line with Norway (39%) and Poland (31%), to facilitate market access by the biosimilar in order to gain real-world experience.

However, any apparent cost advantage must be balanced against the uncertain efficacy and unknown risk from the biosimilar. Product specific data (from IBD trials) will mitigate against this concern.

For more on this, go to **www.bsg.org.uk**

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