BLOCKING THE IMMUNE SYSTEM IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis is caused by the immune system attacking the body. It afflicts around 1% of people in the UK and is now treated with a variety of biologic drugs that dampen the immune system in different ways. By Janna Lawrence.

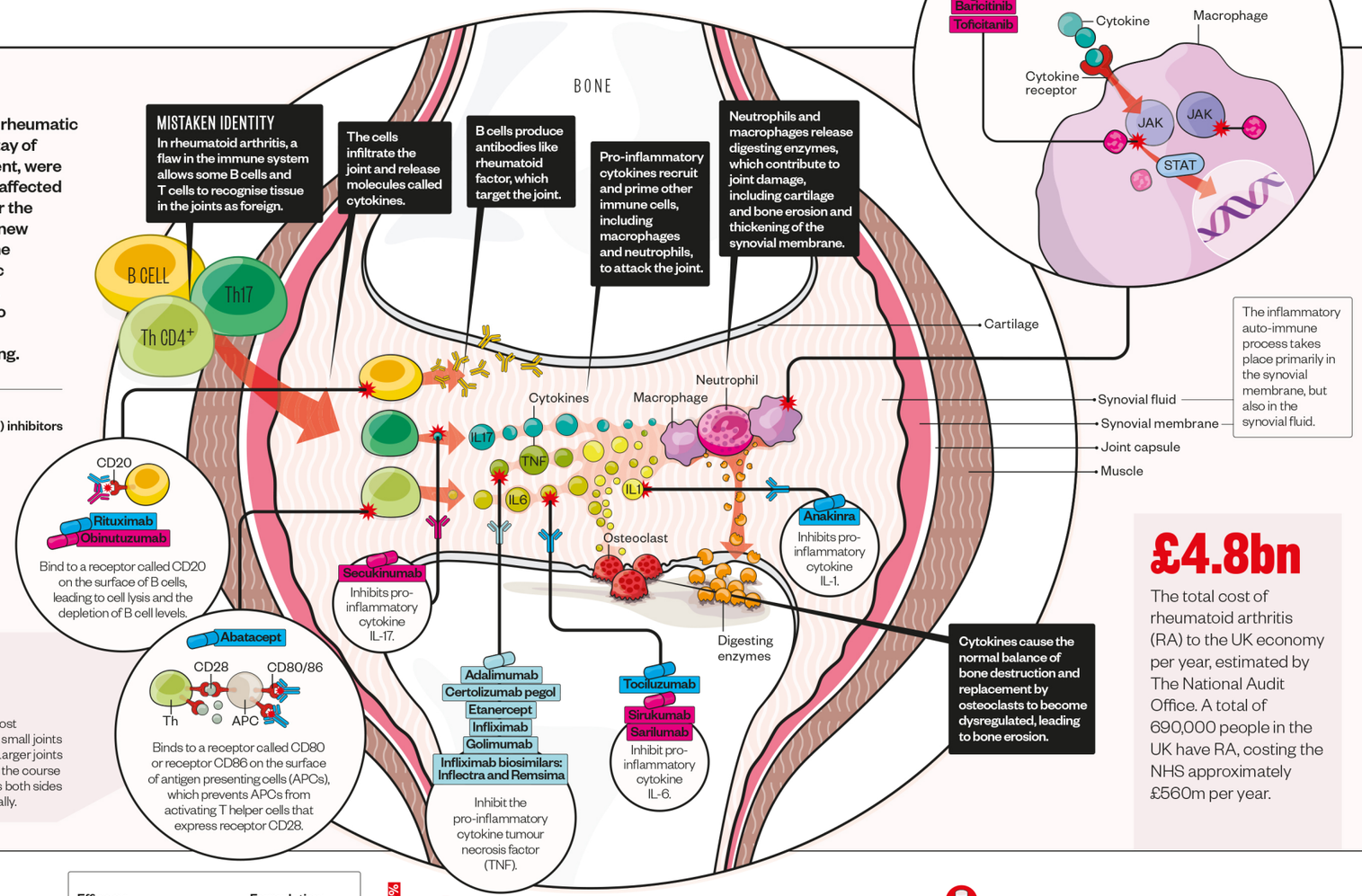
DRUG TARGETS

Oral disease-modifying anti-rheumatic drugs (DMARDs), the mainstay of rheumatoid arthritis treatment, were the first drugs available that affected the immune system. But over the past 15 years, a multitude of new biologic therapies have hit the market, which target specific parts of the immune system. New small molecules are also in development that target intracellular immune signalling.

Tumour necrosis factor (TNF) inhibitors
Other biologics
Pipeline drugs

JOINTS AFFECTED

Rheumatoid arthritis most commonly starts in the small joints of the hands and feet. Larger joints can be affected later in the course of the disease. It affects both sides of the body symmetrically.



The inflammatory auto-immune process takes place primarily in the synovial membrane, but also in the synovial fluid.

£4.8bn

The total cost of rheumatoid arthritis (RA) to the UK economy per year, estimated by The National Audit Office. A total of 690,000 people in the UK have RA, costing the NHS approximately £560m per year.

TREATMENT PATHWAY

Early targeted therapy to rapidly control disease activity in rheumatoid arthritis (RA) is crucial to limiting long-term joint damage. A range of drugs are approved by the National Institute for Health and Care Excellence (NICE) for use within the NHS.

1 DIAGNOSIS
Person diagnosed with rheumatoid arthritis.

2 INITIAL TREATMENT
Prescribe a combination of methotrexate and one other oral DMARD. DMARDs take several weeks to work so a short course of steroids is usually prescribed while the DMARDs take effect.

DISEASE CONTROL? YES → Reduce doses to level that maintains disease control. NO →

3 FIRST-LINE BIOLOGIC
Prescribe a biologic in combination with methotrexate (e.g., adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, tocilizumab or abatacept). Use the least expensive drug first, taking account of administration and drug costs and patient access schemes. Anakinra is not approved by NICE.

DISEASE CONTROL? YES → Reduce doses to level that maintains disease control. NO →

4 SECOND-LINE BIOLOGIC
If there is an inadequate response or intolerance to other drugs, including at least one TNF inhibitor, prescribe rituximab in combination with methotrexate. If rituximab is contraindicated, prescribe another biologic that has not been tried (e.g., adalimumab, etanercept, infliximab or abatacept).

DISEASE CONTROL? YES → Reduce doses to level that maintains disease control. NO → Consider referral for surgery.

SYMPTOM CONTROL

Pain relief: Prescribe paracetamol, codeine or compound analgesics, or non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase (COX)-2 inhibitors at the lowest effective dose for the shortest possible period of time.

Flare-ups: Prescribe short-term glucocorticoids for flare-ups.

DRUG DEVELOPMENT

The first breakthrough in rheumatoid arthritis treatment was methotrexate. Since then, numerous biologics have been approved by the European Medicines Agency for use in combination with methotrexate. The prices are high but efficacy is good for patients who have failed on methotrexate and other oral DMARDs alone. The first biosimilars were approved in 2013, introducing more price competition to the biologics market.

Efficacy:
- Probability of 20% symptom improvement
- Probability of 50% symptom improvement

Formulation:
- Tablet
- Injection
- Infusion

1983: METHOTREXATE
56% / 32%
Brand: generic
Manufacturer: multiple
Average dose: 15mg weekly
Year 1 cost (2016): £43

2000: INFLIXIMAB
70% / 40%
Brand: Remicade
Manufacturer: MSD
Average dose: 3mg/kg, repeated after two weeks, then four weeks, then every eight weeks
Year 1 cost (2016): £10,071

2000: ETANERCEPT
69% / 46%
Brand: Enbrel
Manufacturer: Pfizer
Average dose: 25mg twice weekly or 50mg once weekly
Year 1 cost (2016): £9,295

2003: ADALIMUMAB
57% / 33%
Brand: Humira
Manufacturer: AbbVie
Average dose: 40mg every two weeks
Year 1 cost (2016): £9,155

Prices don't include monitoring costs, VAT or patient access schemes.

2006: RITUXIMAB
51% / 27%
Brand: Mabthera
Manufacturer: Roche
Average dose: 1,000mg two weeks apart, repeated after six months
Year 1 cost (2016): £6,985

2007: ABATACEPT
IV: 56% / SC: 55%
IV: 32% / SC: 34%
Brand: Orencia
Manufacturer: BMS
Average dose: 750mg intravenously every two weeks for three doses, then monthly or 125mg subcutaneous injection weekly
Year 1 cost (2016): £12,701 (intravenous [IV]) £16,632 (subcutaneous [SC])

2009: GOLIMUMAB
62% / 38%
Brand: Simponi
Manufacturer: MSD
Average dose: 50mg once monthly
Year 1 cost (2016): £9,156

2009: TOCILUZUMAB
64% / 40%
Brand: RoActerma
Manufacturer: Roche
Average dose: 8mg/kg every four weeks
Year 1 cost (2016): £10,250

2009: CERTOLIZUMAB PEGOL
72% / 49%
Brand: Cimzia
Manufacturer: UCB
Average dose: 400mg every two weeks for three doses, then 200mg every two weeks
Year 1 cost (2016): £10,368

Efficacy data are from a network meta-analysis, except for rituximab, infliximab and the infliximab biosimilars, which are response rates from single trials.

2013: INFLIXIMAB BIOSIMILAR
73% / 43%
Brand: Remsima
Manufacturer: Napp
Average dose: 3mg/kg, repeated after two weeks, then four weeks then every eight weeks
Year 1 cost (2016): £9,064

2013: INFLIXIMAB BIOSIMILAR
73% / 43%
Brand: Inflectra
Manufacturer: Hospira
Average dose: 3mg/kg, repeated after two weeks, then four weeks then every eight weeks
Year 1 cost (2016): £9,064